Friday, 27 February 2015

Dear Editor,

Please find enclosed the edited revised manuscript in Word format (file name: **15923-review.doc**).

Title: Hepatic inflammatory pseudotumor presenting in an 8-year-old boy: A Case report and Review of Literature

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Name of Journal: World Journal of Gastroenterology

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REVIEWER [1] COMMENTS

1. **(A)** Is CD-25 test routine in your hospital? **(B)** Please explain the reason?

   (A) The following paragraph was added to answer if CD-25 is a routine test:

   [Lines: 238—240]: "Measuring the soluble CD-25 serum level is not a routine practice in our hospital. In fact, globally, the routine use of soluble CD-25 is largely unavailable in the vast majority of laboratories, and its current use is limited to only experimental research purposes."

   (B) The following two paragraphs were added to explain the reason:

   First paragraph [lines: 242—251]: " In our case, the reason for ordering the soluble CD-25 serum-level test was rationalized by 1) its availability at our advanced tertiary-care hospital and, more importantly, 2) the possible differential diagnosis of macrophage activation syndrome (MAS). MAS is a fetal complication of pediatric rheumatic diseases. It occurs most often in children with systemic juvenile idiopathic arthritis (SJIA) and is characterized by the presence of neurologic symptoms, pancytopenia, coagulopathy mimicking disseminated intravascular coagulation (DIC) and hepatic insufficiency. Its presumed pathogenesis is the life-threatening activation and uncontrolled expansion of T-lymphocytes and macrophagic histiocytes, causing excessive hemophagocytosis and cytokine overproduction[19,20]".

   Second paragraph [lines: 253—261]:" Recently, soluble serum CD-25 (the alpha-chain of the IL-2 receptor) has been demonstrated to be a potentially useful marker for identifying early (subclinical) MAS in patients with SJIA[21,22]. Additionally, at the very onset of MAS, patients may experience a paradoxical improvement in the underlying inflammatory disease, with eventual resolution of arthritis signs and symptoms, as well as a rapid decrease in the ESR. The latter phenomenon may be attributed to hypofibrinogenemia due to fibrinogen

consumption and hepatic dysfunction[23]. Despite the high level of soluble CD-25 in the serum, our patient did not adequately meet the other diagnostic criteria for MAS complicating SJRA[24-26]."

— Moreover, the possible differential diagnosis of Macrophage Activation Syndrome (MAS) was also suggested by **[REVIEWER (3); Comment (2)]**.

2. **(A)** Please provide the section image of right hepatic vein thrombosed and **(B)** discuss any relation to the IPT?

(A) Two section images of the right hepatic vein thrombosis were provided:

I. Computed tomography (CT) scan [lines: 137—138]:" In the delayed venous phase, the right hepatic vein was thrombosed, whereas the middle and left hepatic veins were patent **(Figure 1B)**."

II. Magnetic resonance imaging (MRI) scan [Lines: 143—144]:" The right hepatic vein was completely thrombosed up to the inferior vena cava **(Figure 2B)**."

(B) One paragraph was added to discuss the relationship between hepatic IPT and **[hepatic vein thrombosis]** in our case:

[Lines: 263—275]:" In our case, the patient developed right hepatic vein thrombosis, and this event could be attributed to three main reasons. First, hepatic IPTs are characterized by extensive proliferation of multiple inflammatory cells[1] that jointly produce various thrombogenic cytokines, leading to pro-coagulant activity (that is, thrombosis) of the vascular endothelium[27]. Figure 6B shows that the inflammatory cells were concentrated around blood vessels. Second, as revealed by CT (Figure 1A) and MRI (Figure 2A) scans, the hepatic IPT lesion involved the right hepatic lobe (segments V, VI, and VII), which is known to be anatomically drained by the right hepatic vein.

Accordingly, extension of the hepatic IPT lesion (thrombo-embolus) into the right hepatic vein lumen is a plausible reason for the right hepatic vein thrombosis/obstruction. Third, as opposed to the central (hilar) location, the peripheral location of the hepatic IPT (in our case — right lobe) and occurrence of hepatic venous thrombosis/occlusion is a well-documented phenomenon in the literature[13]"

— Moreover, an additional paragraph discussing the relationship between hepatic IPT & **[portal venous thrombosis]** was added:

[Lines: 277—283]:" In our case, the portal vein was unremarkable. Local thrombosis of the portal vein is a well-recognized complication of IPT lesions involving the hepatic hilum rather than the peripheral hepatic parenchyma[13,28,29]. However, although this condition is rare, Fernandes et al. reported the extremely unusual case of extensive portal venous thrombosis and peripheral right hepatic lobe IPT in a 9-year-old boy who presented to an emergency department with a 20-day history of abdominal pain and fever of 2 days' duration[30]"

REVIEWER [2] COMMENTS

1. There is not new knowledge about IPTs.

— There has been not much new knowledge about hepatic IPTs, and this can be attributed to its rarity and low incidence:

[Lines: 95—96]: "As of 2011, fewer than 300 cases of hepatic IPTs have been reported in the medical literature[4]. More specifically, as of 2008, only 35 cases of pediatric (childhood) hepatic IPTs have been reported so far[5]."

[Lines: 236—237]:" Some recent reports of hepatic IPTs in childhood from 2009 to 2014 (n=9) are summarized in Table 1[5,6,30,48-52]" The summary was performed by this manuscript's authors.

— While our presented Case Report does not add much new knowledge, however, it greatly enriches the current lacking literature about pediatric hepatic IPTs, in terms of providing additional clinico-pathological data and validating/invalidating some of the published facts, including and not limited to, associations with autoimmune IgG4-related disease and EBV infection, as well as recurrence and malignant transformations.

[Lines: 174—178]:" Furthermore, the hepatic lesion displayed focal positivity for IgG4 (7 plasma cells/high-power field), which was inadequate for classifying it as an IgG4-related disease (>10 plasma cells/high-power field is required for the diagnosis) (Figure 7B). In situ hybridization ruled out EBV infection."

[Lines: 67—68]:" At the postoperative 4-month follow-up, the patient was asymptomatic without radiological evidence of recurrence."

— Moreover, the following "**recommendations**" were added:

[Lines: 150—152]:" In view of the unremitting FUO, tender hepatomegaly, thrombosed right hepatic vein, nonspecific radiological findings, and high suspicion of a deep-seated underlying infection or malignancy, a right hepatic lobectomy was recommended".

[Lines: 309—314]:" Despite the nonspecific radiologic appearances[7,16,17], it can be concluded that the various imaging modalities may offer valuable clues for diagnosing hepatic IPT in patients with the following characteristics: 1) clinical signs and symptoms of inflammation; 2) laboratory results suggesting inflammation; 3) normal serum tumor

markers such as CEA, CA 19-9 and AFP; and 4) evidence of mass-occupying hepatic lesions on imaging[35]"

[Lines: 342—343]:" Hepatic IPTs should be considered in the differential diagnosis of all pediatric patients presenting with fever of unknown origin (FUO)".

2. If the authors want to emphasize the rare case of hepatic IPT in childhood, the authors should summarize the previous reports of hepatic IPT in childhood.

— As requested, summary was performed in a "Table" format:

[lines: 336—337]:" Some recent reports of hepatic IPTs in childhood from 2009 to 2014 (n=9) are summarized in Table 1[5,6,30,48-52]"

— Moreover, the following sentence was added:

[Lines: 333—334]:" All cases of childhood hepatic IPTs from 1971 to 2008 (n=35) were previously reviewed by Nagarajan et al[5]."

3. The authors should discuss about something new, for example, radiological finding which is specific to IPT.

— Radiological findings in hepatic IPT are largely nonspecific:

[Lines: 219—222]:" However, accurately diagnosing hepatic IPTs can be very challenging because the clinical presentation and radiological appearances are nonspecific and cannot be certainly distinguished from other malignant neoplastic processes[7,16,17]. Further research is needed."

[Lines: 285—289]:" Despite the advances in imaging technologies, distinguishing between IPTs and other focal hepatic lesions continues to be a major challenge[4]. Radiologically, hepatic IPTs may largely mimic other granulomatous lesions (such as

sarcoidosis and tuberculosis) or malignant lesions (such as metastatic tumors, hepatocellular carcinoma, lymphoma, and malignant fibrous histiocytoma)[4].

— However, we described the **most frequent** radiological findings in hepatic IPTs (although nonspecific) on various imaging modalities (ultrasound [US], computed tomography [CT], magnetic resonance imaging [MRI], gadoxetic acid (Gd-EOB)—MRI, and positron emission tomography/computed tomography [PET/CT]):

[Lines: 289—307]:" Hepatic IPTs can present as a single or multi-focal mass with a non-specific radiological appearance[5,7,16,17]. On ultrasound imaging, these lesions may appear hyper-echoic or hypo-echoic, with septations and increased through-transmission[31]. On contrast-enhanced CT imaging, variable patterns of enhancement exist, such as peripheral enhancement with delayed central filling, homogeneous enhancement, heterogeneous enhancement and enhancement of septa. Alternatively, there may be negative enhancement or central necrosis[9,31]. On MRI imaging, these lesions express hyper-intensity and hypo-intensity on T2-attenuated and T1-attenuated scans, respectively[32]. Moreover, the presence of small nodular extensions at the boundary of the hepatic IPT lesions during the hepatobiliary phase of gadoxetic acid (Gd-EOB)—MRI may represent a distinctive radiological finding of hepatic IPT. However, this finding is still investigational and needs to be validated and reproduced in other cases[33]. On fluorodeoxyglucose (FDG) positron imaging tomography/computed tomography (PET/CT) scan, the FDG uptake in hepatic IPTs range from low to high uptake, depending on several factors, such as 1) lesion cellularity, 2) biological behavior, 3) composition and number of inflammatory cells, and 4) degree of inflammatory cell activation[34]. Additionally, FDG PET/CT scans may be valuable for identifying new primary IPTs, loco-regional relapses, and distant metastatic foci[34]."

— Moreover, the following conclusion paragraph about radiologic findings in hepatic IPTs was added:

[Lines: 309—314]:" Despite the nonspecific radiologic appearances[7,16,17], it can be concluded that the various imaging modalities may offer valuable clues for diagnosing hepatic IPT in patients with the following characteristics: 1) clinical signs and symptoms of inflammation; 2) laboratory results suggesting inflammation; 3) normal serum tumor markers such as CEA, CA 19-9 and AFP; and 4) evidence of mass-occupying hepatic lesions on imaging[35]."

REVIEWER [3] COMMENTS

1. The references are not enough new and should follow the recommendations of the journal. I suggest discussing that case in the light of recent data from the literature.

— The major reason for not including enough new references is that there has been not much new knowledge about hepatic IPTs, and this can be attributed to its rarity and low incidence:

[Lines: 95—96]: "As of 2011, fewer than 300 cases of hepatic IPTs have been reported in the medical literature[4]. More specifically, as of 2008, only 35 cases of pediatric (childhood) hepatic IPTs have been reported so far[5]."

— As requested by Peer-Reviewer (2), we summarized the recent childhood hepatic IPTs:

[Lines: 236—237]:" Some recent reports of hepatic IPTs in childhood from 2009 to 2014 (n=9) are summarized in Table 1[5,6,30,48-52]". New references were used, and highlighted in yellow color in the [References List].

- To the best of our knowledge and capabilities, the authors of this manuscript truly attempted to cite the most up-to-date references — whenever available and applicable. However, this was not easily possible due to the rarity of pediatric hepatic IPTs and the few available publications.
- It is important to note that almost all the references we used in our manuscript were leading and persistently highly cited published articles (despite being somehow not enough new).
- Recently published information as well as almost all peer-reviewers' comments were addressed using recent references. Those new information and references were highlighted in yellow color in the [Manuscript Text] and [References List].

2. The authors should also make reference to the differential diagnosis with the macrophage activation syndrome.

- As requested, reference to the suggested differential diagnosis was made and elaborated upon:
- First paragraph [lines: 242—251]: " In our case, the reason for ordering the soluble CD-25 serum-level test was rationalized by 1) its availability at our advanced tertiary-care hospital and, more importantly, 2) the possible differential diagnosis of macrophage activation syndrome (MAS). MAS is a fetal complication of pediatric rheumatic diseases. It occurs most often in children with systemic juvenile idiopathic arthritis (SJIA) and is characterized by the presence of neurologic symptoms, pancytopenia, coagulopathy mimicking disseminated intravascular coagulation (DIC) and hepatic insufficiency. Its

presumed pathogenesis is the life-threatening activation and uncontrolled expansion of T-lymphocytes and macrophagic histiocytes, causing excessive hemophagocytosis and cytokine overproduction[19,20]".

- [Lines: 253—261]:" Recently, soluble serum CD-25 (the alpha-chain of the IL-2 receptor) has been demonstrated to be a potentially useful marker for identifying early (subclinical) MAS in patients with SJIA[21,22] …….. Despite the high level of soluble CD-25 in the serum, our patient did not adequately meet the other diagnostic criteria for MAS complicating SJRA[24-26]."

- Moreover, reference to the suggested differential diagnosis was included in the **Comments** section of manuscript:

  [Lines: 254—357]:"Differential diagnosis: Underlying deep-seated infection, abscess, granulomatous lesions (such as: sarcoidosis and tuberculosis), malignant lesions (such as: metastatic tumor and malignant fibrous histiocytoma) and macrophage activation syndrome."

3. There are also some spelling mistakes which must be corrected [ex erythrocyte sedimentation rate (ESR) of 140 ml/hr].

- This unintended spelling mistake was corrected:

  [Lines: 120—121]:"Other laboratory tests showed high erythrocyte sedimentation rate (ESR) of 140 mm/hr…"

- The revised manuscript was submitted to **American Journal Experts** to achieve the World Journal of Gastroenterology's language status of **Grade A** (no language polishing required) that allows a manuscript to be given priority for acceptance and publication consideration.

- The revised manuscript has received the requested "**Editorial Certificate**" (attached).
- Certificate Verification Key: 8578-15D1-3CAC-1814-9EB3.

EDITOR COMMENTS

Note: For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Case Report'

- The revised manuscript was submitted to **American Journal Experts** to achieve the World Journal of Gastroenterology's language status of **Grade A** (no language polishing required) that allows a manuscript to be given priority for acceptance and publication consideration.
- The revised manuscript has received the requested "**Editorial Certificate**" (attached).
- Certificate Verification Key: 8578-15D1-3CAC-1814-9EB3.

1. **Comment [q1]:** The ethic approval document(s)/letter(s) must be provided in a PDF format, and each statement must also be mentioned as a footnote in the manuscript text.
   - [Lines: 25—27]:"Ethics approval: The publication of this manuscript has been approved by the Research Advisory Council (RAC) at the King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia".
   - The PDF file was attached.

2. **Comment [q2]:** The registration information must be provided in a PDF format, and the registered URL and registration identification number must also be mentioned as a footnote in the manuscript text.

Sample wording: This study is registered at [URL]. The registration identification number is [registration identification number].

— [Line 29]:"Not applicable"

3. **Comment [q3]:** This (Conflicts-of-Interest) file must be signed by the corresponding author and provided in a PDF format, and the statement must also be mentioned as a footnote in the manuscript text.

   Sample wording: [Name of individual] has received fees for serving as a speaker, a [position; such as consultant and/or an advisory board member] for [name(s) of organization(s)]. [Name of individual] has received research funding from [name(s) of organization(s)]. [Name of individual] is an employee of [name(s) of organization(s)]. [Name of individual] owns stocks and/or shares in [name(s) of organization(s)]. [Name of individual] owns patent [patent identifier information (including patent number, two-letter country code, and kind code) and a brief description].

   — [Lines: 34—36]:" Conflict-of-interest: The authors declare no conflicts of interest regarding the production of this article. The authors have no personal financial or institutional interests in any of the drugs, materials, or devices described in this article".

   — The PDF file was attached.

4. **Comment [q4]:** Audio Core Tip

   In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:

   Acceptable file formats: .mp3, .wav, or .aiff

   Maximum file size: 10 MB

To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

— Sorry, the Audio Core Tip was not uploaded.

5. **Comment [q5]:** Please reformat all the reference numbers like this. Please check throughout. Thank you!

— As requested, all reference numbers were reformatted throughout the manuscript. That is, superscript square brackets**.**

6. **Comment [q6]:** Please write this part according to the template. Thank you!

— The Comments section was written and included.

— [Lines: 347—394]:

Case characteristics

An 8-year-old boy presented to the clinic with a 3-month history of a tender hepatic mass (hepatomegaly) and fever of unknown origin (FUO).

Clinical diagnosis

The physical examination revealed tender hepatomegaly; the liver was palpable 2 cm below the costal margin.

Differential diagnosis

Underlying deep-seated infection, abscess, granulomatous lesions (such as sarcoidosis and tuberculosis), malignant lesions (such as metastatic tumors and malignant fibrous histiocytoma) and macrophage activation syndrome.

Laboratory diagnosis

High erythrocyte sedimentation rate (ESR) of 140 mm/hr and C-reactive protein (CRP) level of 246 mg/l; normal tumor markers (alpha-fetoprotein [AFP], carcinoembryonic antigen [CEA], and cancer antigen [CA] 19-9); and negative workup for hepatitis, echinococcus, brucella, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV) and hemophagocytic lymphohistiocytosis (HLH).

Imaging diagnosis

Contrast-enhanced computed tomography (CT) revealed a 6.3 x 5.1 x 5.5 cm, relatively well-defined, hypodense lesion with internal enhancement involving the right hepatic lobe (segments V, VI and VII), as well as a thrombosed right hepatic vein; magnetic resonance imaging (MRI) yielded similar yet nonspecific findings.

Pathological diagnosis

Microscopically, the right hepatectomy tissue exhibited a mixture of inflammatory cells (histiocytes, plasma cells, mature lymphocytes, and occasional multinucleated giant cells) in a background of dense fibrous tissue without granulomas, whereas immunohistochemical staining showed negativity for SMA, ALK-1, CD-21 and CD-23 but diffuse positivity for CD-68 and focal positivity for IgG-4.

Treatment

The patient underwent a right hemi-hepatectomy.

Related reports

Pediatric (childhood) hepatic inflammatory pseudotumors (IPTs) are exceedingly uncommon, and fever of unknown origin is a rare presenting clinical symptom.

Term explanation

Inflammatory pseudotumors, also known as inflammatory myofibroblastic tumors, are rare, benign lesions characterized histologically by the proliferation of inflammatory cells

(for example, neutrophils, eosinophils, lymphocytes, plasma cells, histiocytes, and multinucleated giant cells), myofibroblasts and spindle-shaped cells.

Experiences and lessons

Although rare, hepatic IPTs should be suspected in pediatric patients with the following characteristics: 1) clinical and laboratory findings of inflammation/infection, 2) normal serum tumor markers such as AFP, CEA, and CA 19-9, and 3) evidence of liver mass-occupying lesions on imaging.

Peer-review

This article presents a rare yet challenging case of pediatric hepatic IPT. This case report highlights that—in view of FUO, tender hepatomegaly, a thrombosed right hepatic vein, nonspecific radiological findings, and a high suspicion of deep-seated underlying infection or malignancy—surgical resection is the recommended management strategy.

7. **Comment [q7]:** Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

PMID (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed) DOI (http://www.crossref.org/SimpleTextQuery/) (Please begin with DOI: 10.**)

For those references that have not been indexed by PubMed, a printed copy of the first page of the full reference should be submitted.

- All references are PubMed-Indexed.
- For all references, PMID citations were included.
- For all references, DOI citations were included, except for 5 references, namely: **[3]**, **[12]**, **[18]**, **[32]** and **[47]** as DOI citations could not be found (to the best of our knowledge).

- For all references, all authors' names were listed.
- All newly added references were highlight in yellow color.

8. **Comment [q8]:** Please list all authors' name of all references.

- All authors' names of all references were listed.

AUTHORS COMMENTS

- All newly added/modified information and references were highlight in yellow color.
- All citations and references were double-checked to make sure they are accurate and correspond to each others.
- Many thanks to the peer-reviewers for their critical evaluation and valuable comments to make our manuscript more appealing.
- We did our maximum best to address all peer-reviewers' comments adequately.
- All provided figures are of high-resolution (300 dpi).
- We look forward to publishing our manuscript at your well-respected WJG.

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